Mechanisms of Resistance in Protozoan Parasites

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Malaria is the most significant disease caused by a protozoan parasite, claiming the lives of over two million people annually. The emergence of drug resistant human malaria, *Plasmodium falciparum*, has made attempts to combat this health problem increasingly difficult. Although the mechanisms of this resistance have not been fully elucidated, several protozoan parasites express genes which are proposed to efflux drug as a mechanism of resistance. Two of these genes, *lemdr1* of *Leishmania enriettii* and *pfmdr1* of *P. falciparum*, are part of the ATP-Binding Cassette (ABC) gene family, whose members are thought to be involved in drug resistance and cell communication, encoding proteins proposed to export molecules from cells. To address the functional role of the *lemdr1* and *pfmdr1* genes in drug resistance, three general approaches have been taken in our laboratory. The first approach is heterologous expression of these genes and complementation of a functional mutation. It has been shown that the expression of some members of the ABC gene family, the mouse *mdr3* gene and the human cystic fibrosis gene, can complement the *ste6* gene of *Saccharomyces cerevisiae*, a gene which is involved in a-factor pheromone export, by restoring a mating phenotype in an *ste6* deleted strain. This system was used to address a possible functional role of *pfmdr1* or *lemdr1* in export or efflux. In addition to heterologous transformation, homologous transformation and site specific mutagenesis can be used to demonstrate a functional role of these protozoan genes in drug resistance. Homologous transformation of the *lemdr1* gene into drug sensitive *L. enriettii* along with site specific mutagenesis of this gene has been used as a second approach to establish a functional role of this gene product in drug resistance. Transformation of drug sensitive parasites with the *lemdr1* gene can confer a drug resistance phenotype and site specific mutagenesis can abolish this phenotype. A third approach is to develop a homologous transformation system in malaria to address the possible role of *pfmdr1* in drug resistant *P. falciparum*. Development of such a system will establish a functional role of this gene in the drug resistance phenotype. Through these efforts, we hope to demonstrate a functional role for the *pfmdr1* gene of *P. falciparum* in a mechanism of drug resistance as has been shown for the *lemdr1* gene of *L. enriettii*.

Source: https://www.industrydocuments.ucsf.edu/docs/rgmv0000